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(54) Title: NOVEL ANTI-ADHESIVE COMPOUNDS AND USES THEREOF

(57) Abstract: Compounds which exhibit anti-adhesive properties are described. The compounds may be monomers or polymers. Methods for treating receptor mediated diseases are provided using compounds of the invention. Further methods are provided for crop protection, medical devices and anti-fouling.

NOVEL ANTI-ADHESIVE COMPOUNDS AND USES THEREOF

INTRODUCTION

Adhesion of biologics to a surface can lead to harmful effects upon the surfaces, referred to as "fouling" of the surface. A wide variety of biologics can contribute to fouling, including bacteria, fungi, algae, protozoans, and invertebrates. Fouling of surfaces may have damaging consequences for surfaces in a number of contexts, including surfaces submerged in liquids, exposed to aqueous vapors, or implanted in human or animal bodies.

In a health-related environment, fouling can result in biofilm formation. Biofilm formation is understood to cause local contamination of an affected area with potential for invasive local infection and for systemic infection. Microorganisms may damage tissues in at least three ways: 1) they can enter or contact host cells and directly cause cell death; 2) they can release endotoxins or exotoxins that kill cells at a distance, release enzymes that degrade tissue components, or damage blood vessels and cause ischemic necrosis; and 3) they can induce host-cellular responses that, although directed against the invader, may cause additional tissue damage, including suppuration, scarring and hypersensitivity reactions. An infection, whether local or systemic, represents the penetration of microorganisms into a host with the production of tissue damage or the elicitation of host defense mechanisms or both, leading to clinically identifiable symptoms. Common local symptoms can include pain, tenderness, swelling and interference with function. Common systemic symptoms can include fever, malaise and hyperdynamic cardiovascular effects. Massive bloodstream invasion by infectious agents can rapidly become fatal.

When an infection has its origins in a biofilm surrounding an object in the body, whether a naturally occurring object or a foreign one, the infection often cannot be controlled without removing that object. If the object is naturally occurring, like devascularized or necrotic tissue, it is removed surgically via a process called debridement. If the object is a foreign one, such as a medical device, it is removed entirely. At times, a rim of tissue must be removed along with the contaminated object to ensure maximal removal of contaminating material. If the material being removed is essential for health, a similar article may need to be replaced in the same location; the replacement article will be especially prone to infection because of the residual microorganisms in the area.

Biofilm formation with health implications can involve those surfaces in all health-related environments, including surfaces found in medical environments and those surfaces in industrial or residential environments that are involved in functions essential to well-being like nutrition, sanitation and the prevention of disease.

In addition to being susceptible to infection, implantable medical devices may be thrombogenic. For example, it has been shown that contact with metal, glass, plastic or other similar surfaces can induce blood to clot. In this regard, thrombogenesis is a form of abiologic fouling also amenable to treatment by the antifouling compositions of the invention described herein.

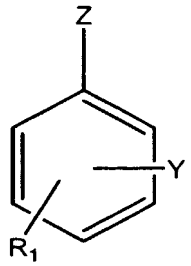
Adhesion of pathologic biologics to the surface of host cells is often a required step in the pathogenesis of disease. Such biologics adhere to cell surfaces through interactions involving surface-bound receptors. Substances that preferentially bind to these receptors or otherwise block access to them by pathologic biologics, such as the compounds of the instant invention, may have use in preventing initiation of cellular infection.

Antifouling compounds, such as the compositions of the instant invention, also have utility as environmentally benign crop protection agents by preventing attack of various fungi species upon seeds, seedlings, and mature crop plants, and bacteria.

By interfering with the attachment of organisms to surfaces, antifouling agents may have broad applicability in effectively inhibiting a variety of organisms that contribute to the formation of biofilms or are otherwise involved with biofouling. These compounds may also be environmentally safe, as they may naturally degrade into carbon dioxide and water, or simple organic acids.

SUMMARY OF INVENTION

In one aspect, the instant invention includes compounds having the structure **1**:



1

wherein:

Y represents alkoxy, -OH, sulfonate, sulfate, sulfonyl, sulfoxido, -O-(aryl), -O-(acyl),
-O-(sulfonyl), trifluoro-methanesulfonyl, or methanesulfonyl;

R_1 is absent or present 1, 2, or 3 times;

Z represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

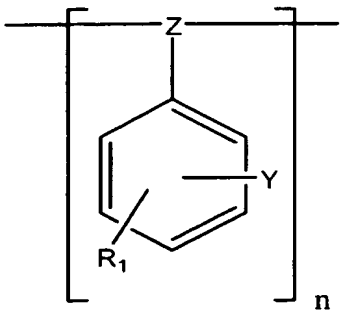
R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

R_1 represents for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

m is an integer in the range 0 to 8 inclusive; and salts thereof.

In one embodiment, Y represents sulfonate, sulfate, sulfonyl, sulfoxido, trifluoro-methanesulfonyl, or methanesulfonyl. In another embodiment, R_1 is absent. In yet another embodiment Z represents alkyl or alkenyl.

In another aspect, the instant invention relates to polymeric compounds which comprise a monomeric unit represented by structure **2**:



2

wherein:

Y represents alkoxy, -OH, sulfonate, sulfate,sulfonyl, sulfoxido, -O-(aryl), -O-(acyl), -O-(sulfonyl), trifluoro-methanesulfonyl, or methanesulfonyl;

R_1 is absent or present 1, 2, or 3 times;

Z represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

R_1 represents for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

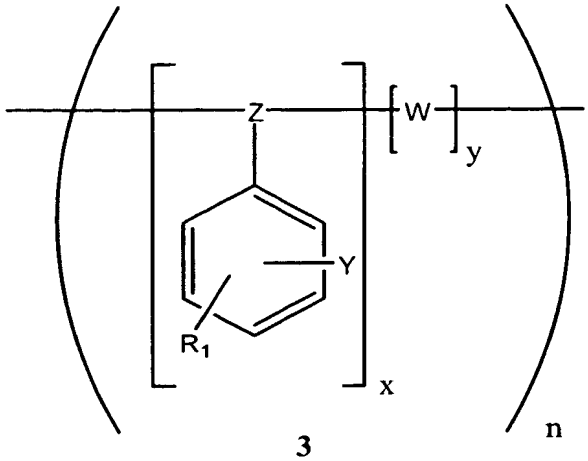
m is an integer in the range 0 to 8 inclusive;

n is an integer from about 2 to about 1000; and the salts thereof.

In one embodiment, Y represents sulfonate, sulfate, sulfonyl, sulfoxido, trifluoro-methanesulfonyl, or methanesulfonyl. In another embodiment, R_1 is absent. In yet another embodiment Z represents alkyl or alkenyl.

In one embodiment, the polymer of structure **2** further comprises a monomeric unit comprising a divalent organic group.

In another embodiment, the instant invention features polymeric compounds comprising a monomeric unit represented by structure **3** :



3

wherein

Y represents alkoxy, -OH, sulfonate, sulfate, sulfonyl, sulfoxido, -O(aryl), -O(acyl), -O(sulfonyl), trifluoro-methanesulonyl, or methanesulfonyl;

R_1 is absent or present 1, 2, or 3 times;

Z represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

W represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

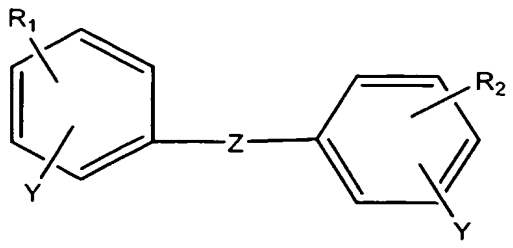
R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

m is an integer in the range 0 to 8 inclusive;

R_1 represents for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

x, y, and n are independently integers from about 1 to about 1000; and the salts thereof.

In yet another aspect, the instant invention relates to compounds having the structure **4**:



4

wherein:

Y represents independently for each occurrence alkoxy, -OH, sulfonate, sulfate, sulfonyl, sulfoxido, -O(aryl), -O(acyl), -O-(sulfonyl), trifluoro-methanesulfonyl, or methanesulfonyl;

R_1 is absent or present 1, 2, or 3 times;

R_2 is absent or present 1, 2, or 3 times;

Z represents optionally substituted alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

R_1 and R_2 represent for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

m is an integer in the range 0 to 8 inclusive; and salts thereof.

In another aspect the invention features methods for treating receptor-mediated diseases utilizing the pharmaceutical compounds of the invention. In addition, many of the compounds of the invention are small molecules and may be administered orally.

In another aspect of the invention, a compound represented by **1**, **2**, **3**, **4**, **5** may be used for crop protection.

In another aspect, the instant invention features medical devices and products comprised of a compound having the structure **1**, **2**, **3**, **4**,or **5**.

In another aspect, the instant invention features antifouling compounds having the structure **1**, **2**, **3**, **4** or **5**.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the basic structure of molecules derived from the combinatorial library.

Figure 2 depicts examples of building blocks that may be sulfonated to produce sulfoxy ester functional groups and examples of spacer building blocks that serve to physically separate each functional group.

Figure 3a shows an example of a number of sulfoxy ester compounds in a combinatorial library.

Figure 3b shows examples of sulfoxy ester compounds in a combinatorial library.

Figure 4 shows a strategy for solid phase synthesis.

Figure 5 depicts a strategy for screening combinatorial libraries for novel non-adhesions.

DETAILED DESCRIPTION

Disclosed herein are novel anti-adhesive compounds for use on surfaces susceptible to adhesion by various biologics. Included among these compounds are esters of coumaric acid, mixed esters of coumaric acid and zosteric acid, and several other classes of compounds as described in the Examples. Such "antifouling" substances may be employed to prevent damage by biologics to such surfaces, prevent formation of biofilms on such surfaces, prevent infection by biologics of such surfaces, suppress thrombogenic properties of such surfaces, and other uses readily apparent to those skilled in the appropriate arts.

Another important property of the compounds of the instant invention is their ability to affect the agglutination of bacterial and mammalian cells. The affects of these compounds on cell agglutination may involve the blocking of certain cell surface receptors and the activation of others - such as those involved in the attachment to extracellular surfaces and which thereby mediate fouling. Thus, these compounds may possess many of the activities of naturally-occurring proteins and glycoproteins which bind to sites on the surface of a cell and thereby affect cell/cell interactions.

The instant compounds interfere with the attachment of organisms to surfaces, thereby having broad applicability in effectively inhibiting the attachment of a variety of

organisms. In addition, the compounds are relatively safe for wide-spread environmental use, as they may naturally degrade into carbon dioxide and water, or simple organic acids.

In addition, certain compounds of the invention have a relatively short half-life after release, rendering them particularly well-suited for widespread environmental use.

Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are described below.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Exemplary heteroatoms are boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "electron-withdrawing group" is recognized in the art, and denotes the tendency of a substituent to attract valence electrons from neighboring atoms, i.e., the substituent is electronegative with respect to neighboring atoms. A quantification of the level of electron-withdrawing capability is given by the Hammett sigma (σ) constant. This well known constant is described in many references, for instance, J. March, Advanced Organic Chemistry, McGraw Hill Book Company, New York, (1977 edition) pp. 251-259. The Hammett constant values are generally negative for electron donating groups ($\sigma[P] = -0.66$ for NH_2) and positive for electron withdrawing groups ($\sigma[P] = 0.78$ for a nitro group), $\sigma[P]$ indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl, formyl, sulfonyl, trifluoromethyl, cyano, chloride, and the like. Exemplary electron-donating groups include amino, methoxy, and the like.

The term "alkyl" refers to the radical of saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In one embodiment, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and in another embodiment, 20 or fewer. Likewise, exemplary cycloalkyls have from 3-10 carbon atoms in their ring structure, and in another embodiment, have 5, 6 or 7 carbons in the ring structure.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein means an alkyl group, as defined above, but having from one to ten carbons, and in one

embodiment, from one to six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. In one embodiment, alkyl groups are lower alkyls. In one embodiment, a substituent designated herein as alkyl is a lower alkyl.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term "aryl" as used herein includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms *ortho*, *meta* and *para* apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and *ortho*-dimethylbenzene are synonymous.

The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can also be polycycles. Heterocyclyl groups include, for

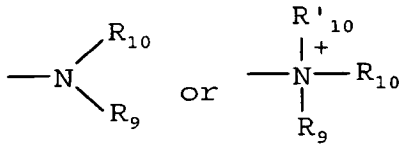
example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The terms "polycyclyl" or "polycyclic group" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbocycle", as used herein, refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

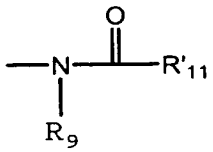
As used herein, the term "nitro" means $-NO_2$; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means $-SO_2-$.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that can be represented by the general formula:



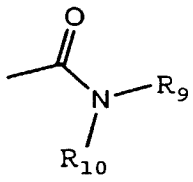
wherein R_9, R_{10} and R'_{10} each independently represent a group permitted by the rules of valence.

The term "acylamino" is art-recognized and refers to a moiety that can be represented by the general formula:



wherein R_9 is as defined above, and R'_{11} represents a hydrogen, an alkyl, an alkenyl or $-(CH_2)_m-R_8$, where m and R_8 are as defined above.

The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:

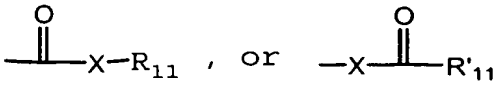


wherein R_9, R_{10} are as defined above. In one embodiments, of the amide will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In preferred embodiments, the "alkylthio" moiety is represented by

one of -S-alkyl, -S-alkenyl, -S-alkynyl, and -S-$(CH_2)_m$-R_8, wherein m and R_8 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

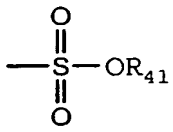
The term "carbonyl" is art recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond or represents an oxygen or a sulfur, and R_{11} represents a hydrogen, an alkyl, an alkenyl, -$(CH_2)_m$-R_8 or a pharmaceutically acceptable salt, R'_{11} represents a hydrogen, an alkyl, an alkenyl or -$(CH_2)_m$-R_8, where m and R_8 are as defined above. Where X is an oxygen and R_{11} or R'_{11} is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R_{11} is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R_{11} is a hydrogen, the formula represents a "carboxylic acid". Where X is an oxygen, and R'_{11} is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X is a sulfur and R_{11} or R'_{11} is not hydrogen, the formula represents a "thiolester." Where X is a sulfur and R_{11} is hydrogen, the formula represents a "thiolcarboxylic acid." Where X is a sulfur and R_{11}' is hydrogen, the formula represents a "thiolformate." On the other hand, where X is a bond, and R_{11} is not hydrogen, the above formula represents a "ketone" group. Where X is a bond, and R_{11} is hydrogen, the above formula represents an "aldehyde" group.

The terms "alkoxyl" or "alkoxy" as used herein refers to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as can be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, -O-$(CH_2)_m$-R_8, where m and R_8 are described above.

The term "sulfonate" is art recognized and includes a moiety that can be represented by the general formula:

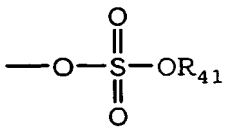


in which R_{41} is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

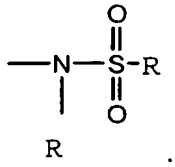
The abbreviations Me, Et, Ph, Tf, Nf, Ts, Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the *Journal of Organic Chemistry*; this list is typically presented in a table entitled Standard List of Abbreviations. The abbreviations contained in said list, and all abbreviations utilized by organic chemists of ordinary skill in the art are hereby incorporated by reference.

The term "sulfate" is art recognized and includes a moiety that can be represented by the general formula:

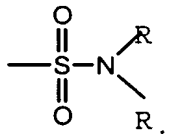


in which R_{41} is as defined above.

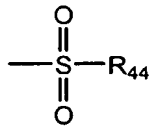
The term "sulfonylamino" is art recognized and includes a moiety that can be represented by the general formula:



The term "sulfamoyl" is art-recognized and includes a moiety that can be represented by the general formula:

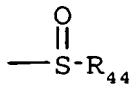


The term "sulfonyl", as used herein, refers to a moiety that can be represented by the general formula:



in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

The term "sulfoxido" as used herein, refers to a moiety that can be represented by the general formula:



in which R_{44} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aralkyl, or aryl.

Analogous substitutions can be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

As used herein, the definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

The phrase "protecting group" as used herein means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991).

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the

racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Contemplated equivalents of the compounds described above include compounds which otherwise correspond thereto, and which have the same general properties thereof (e.g., functioning as precursors), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound to function as precursors of radiolabelled compounds. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

An "aprotic solvent" means a non-nucleophilic solvent having a boiling point range above ambient temperature, preferably from about 25°C to about 190°C, more preferably from about 80°C to about 160°C, most preferably from about 80°C to 150°C, at atmospheric pressure. Examples of such solvents are acetonitrile, toluene, DMF, diglyme, THF or DMSO.

"Biological activity" or "bioactivity" or "activity" or "biological function", which are used interchangeably, for the purposes herein means an effector or antigenic function that is directly or indirectly performed by a compound of the invention or a fragment thereof.

The term "bioavailable" is meant to refer to an appropriate location or orientation of a compound for performance of the compounds' bioactivity.

"Biofilm" refers to an accumulation of organisms on a surface. A mature biofilm can comprise a colony of microorganisms resident upon a surface surrounded by an exopolysaccharide.

"Biofilm resistant" or "antifouling" refers to inhibition or decrease in the amount of biofouling organisms that attach and/or grow.

The term "half-life" refers to the amount of time required for half of a compound to be eliminated or degraded by natural processes

The terms "infectious microorganisms" or "infectious agents" as used herein refers to disease causing or contributing bacteria (including gram-negative and gram-positive organisms, such as *Staphylococci sps.* (e.g. *Staphylococcus aureus*, *Staphylococcus epidermis*), *Enterococcus sp.* (*E. faecalis*), *Pseudomonas sp.* (*P. aeruginosa*), *Escherichia sp.* (*E. coli*), *Proteus sp.* (*P. mirabilis*)), fungi (including *Candida albicans*), viruses (including HIV, HCV, CMV, HBV) and protists (*e.g. Spirochaete spp., Treponema spp..*).

A "pharmaceutically effective amount" refers to an appropriate amount to obtain a therapeutic effect. Toxicity and therapeutic efficacy of compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50 The effective amount may vary within a range depending upon the dosage form employed and the route of administration utilized. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture.

A "polar, aprotic solvent" means a polar solvent as defined above which has no available hydrogens to exchange with the compounds of this invention during reaction, for example DMF, acetonitrile, diglyme, DMSO, or THF.

A "polar solvent" means a solvent which has a dielectric constant ( ) of 2.9 or greater, such as DMF, THF, ethylene glycol dimethyl ether (DME), DMSO, acetone, acetonitrile, methanol, ethanol, isopropanol, n-propanol, t-butanol or 2-methoxyethyl ether. Preferred solvents are DMF, DME, NMP, and acetonitrile.

The term "solid support" includes insoluble, functionalized, polymeric materials to which library members or reagents may be attached, with or without a linker, allowing them to be readily separated, for example by filtration, centrifugation, from, for example, excess reagents, soluble reaction by-products, or solvents.

A "sulfate binding moiety" refers to a moiety that is capable of binding or otherwise associating with a sulfate or sulfonate group.

"Sustained release" or "controlled release" refers to a relatively constant or prolonged release of a compound of the invention from a surface. This can be accomplished through the use of diffusional systems, including reservoir devices in which a core of a compound of the invention is surrounded by a porous membrane or layer, and also matrix devices in which the compound is distributed throughout an inert matrix. Materials which may be used to form reservoirs or matrices include silicones, acrylates, methacrylates, vinyl compounds such as polyvinyl chloride, olefins such as polyethylene or polypropylene, fluoropolymers such as polytetrafluorethylene, and polyesters such as terephthalates. The diffusional systems may be molded into a film or other layer material which is then placed in adherent contact with the structure intended for underwater use. Alternatively, the compounds of the invention may be mixed with a resin, e.g., polyvinyl chloride and then molded into a formed article, which integrally incorporates the compound to form a structure having a porous matrix which allows diffusion of the compound, or a functional portion thereof, into the surrounding environment. Microencapsulation techniques can also be used to maintain a sustained focal release of a compound of the invention. Microencapsulation may also be used for providing improved stability. The encapsulated product can take the form of for example, spheres, aggregates of core material embedded in a continuum of wall material, or capillary designs. The core material of a microcapsule containing a sulfate ester AF agent may be in the form of a liquid droplet, an

emulsion, a suspension of solids, a solid particle, or a crystal. The skilled artisan will be aware of numerous materials suitable for use as microcapsule coating materials, including, but not limited to, organic polymers, hydrocolloids, lipids, fats, carbohydrates, waxes, metals, and inorganic oxides. Silicone polymers are the most preferred microcapsule coating material for treatment of surfaces. Microencapsulation techniques are well known in the art and are described in the Encyclopedia of Polymer Science and Engineering, Vol. 9, pp. 724 et seq. (1989) hereby incorporated by reference.

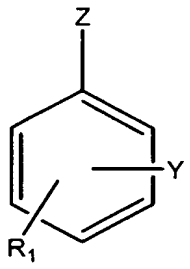
The term "treating" as used herein is intended to encompass curing as well as ameliorating at least one symptom of the condition or disease.

"Plant component" refers to a portion or part of a plant. Examples include: seeds, roots, stems, vascular systems, fruits (further including pip fruits (e.g. apples, pears, quinces)), citrus fruits (oranges, lemons, limes, grapefruits, mandarins, nectarines), stone fruits (peaches apricots, plums, cherries, avocados, grapes), berries (strawberries, blueberries, raspberries, blackberries)), leaves, grains and vegetables.

A "plant pathogen" refers to an organism (bacteria, virus, protist, algae or fungi) that infects plants of plant components. Examples include molds, fungi and rot that typical use spores to infect plants or plant components (e.g fruits, vegetables, grains, stems, roots). Spores must recognize the host, attach, germinate, penetrate host tissues, and proliferate hyphae that will allow the fungus access to nutrients for growth and reproduction. Examples include: Botrytis sp. (B. cinerea), Penicillium sp. (P. expansum, P. italicum, P. digitalum), Rhizopus sp. (R. sulonifer, R. nigricans), Alternaria sp. (A. alternata, A. solani), Diploidia sp. (Diploidia natalenses), Monilinia sp. (M. fructicola), Pseudomonas sp. (P. cepacia) Xanthomonas sp., Erwinia sp. and Corynebacterium. Cladosporium sp. (C. fulva), Phytophtora sp. (P. infestans), Colletotricum spp. (C. coccoides C. fragariae, C. gloesporioides), Fusarium spp. (F. lycopersici), Verticillium spp. (V. alboatrum, V. dahliae), Unicula spp. (U. necator), Plasmopara spp. (P. viticola), Guignardia spp. (G. bidwellii), Cercospora spp. (C. arachidicola), Scelrotinia spp. (S. scerotiorum), Puccinia spp. (P. arachidis), Aspergillus spp. (A. flavus), Venturia spp (V. inaequalis,) Podosphaera spp. (P. leucotricha), Pythiun spp., Sphaerotheca (S. macularis) and Bacillus spp. (B. subitlis)

Compounds

In one aspect, the instant invention includes compounds having the structure **1**:



1

wherein

Y represents alkoxy, -OH, sulfonate, sulfate, sulfonyl, sulfoxido, -O-(aryl), -O-(acyl), -O(sulfonyl) , trifluoro-methanesulfonyl, or methanesulfonyl;

R_1 is absent or present 1, 2, or 3 times;

Z represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

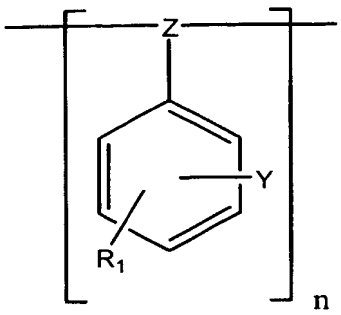
R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl; and

R_1 represents for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino) alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

m is an integer in the range 0 to 8 inclusive; and salts thereof.

In one embodiment, Y represents sulfonate, sulfate, sulfonyl, sulfoxido, trifluoro-methanesulfonyl, or methanesulfonyl. In another embodiment, R_1 is absent. In yet another embodiment Z represents alkyl or alkenyl.

In another aspect, the instant invention relates to polymeric compounds comprising a monomeric unit represented by the following structure **2**:



2

wherein

Y represents alkoxy, -OH, sulfonate, sulfate, sulfonyl, sulfoxido, -O-(aryl), -O-(acyl), -O-(sulfonyl), trifluoro-methanesulonyl, or methanesulfonyl;

R_1 is absent or present 1, 2, or 3 times;

Z represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

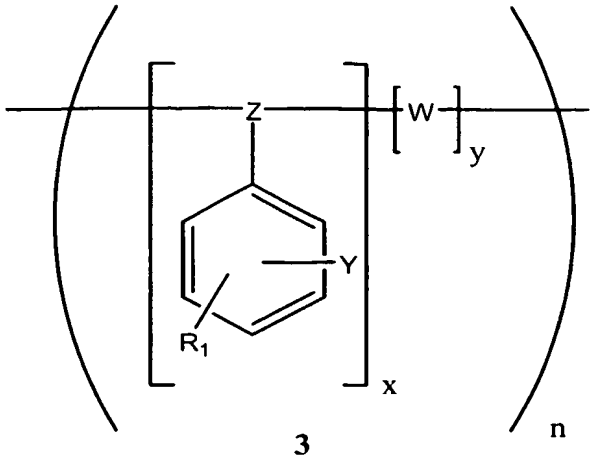
R_1 represents for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy ;

m is an integer in the range 0 to 8 inclusive; and

n is an integer from 2 to about 1000; and the salts thereof.

In one embodiment, Y represents sulfonate, sulfate, sulfonyl, sulfoxido, trifluoro-methanesulfonyl, or methanesulfonyl. In another embodiment, R_1 is absent. In yet another embodiment Z represents alkyl or alkenyl

In one embodiment, the polymer of structure **2** further comprises monomeric units comprising a divalent organic group. In another embodiment, the instant invention features polymeric compounds comprising a monomeric unit represented by structure **3** :



3

wherein

Y represents alkoxy, -OH, sulfonate, sulfate, sulfonyl, sulfoxido, -O(aryl), -O(acyl), -O(sulfonyl), trifluoro-methanesulfonyl, or methanesulfonyl;

R_1 is absent or present 1,2, or 3 times;

Z represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

W represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

m is an integer in the range 0 to 8 inclusive;

R_1 represents for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

x, y, and n are independently integers from about 2 to about 1000; and the salts thereof.

In certain embodiments, the polymers are comprised almost entirely, if not entirely, of the same subunit. Alternatively, in other embodiments, the polymers may be copolymers, in which different subunits and/or other monomeric units are incorporated into the polymer. In certain instances, the polymers are random copolymers, in which the different subunits and/or other monomeric units are distributed randomly throughout the polymer chain. For

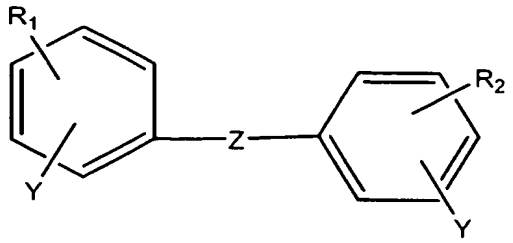
example, the polymer having units of formula **2** and **3** may consist of effectively only one type of such subunit, or alternatively two or more types of such subunits. In addition, the polymer may contain monomeric units other than those subunits represented by formula **2** and **3**.

In other embodiments, the different types of monomeric units, be they one or more subunits depicted by the subject formulas or other monomeric units, are distributed randomly throughout the chain. In part, the term "random" is intended to refer to the situation in which the particular distribution or incorporation of monomeric units in a polymer that has more than one type of monomeric units is not directed or controlled directly by the synthetic protocol, but instead results from features inherent to the polymer system, such as the reactivity, amounts of subunits and other characteristics of the synthetic reaction or other methods of manufacture, processing or treatment.

In certain embodiments, the subject polymers may be cross-linked. For example, substituents of the polymeric chain, may be selected to permit additional inter-chain cross-linking by covalent or electrostatic (including hydrogen-binding or the formation of salt bridges), e.g., by the use of a organic residue appropriately substituted.

The ratio of different subunits in any polymer as described above may vary. For example, in certain embodiments, polymers may be composed almost entirely, if not entirely, of a single monomeric element, such as a subunit depicted in formula **2** and **3**. Alternatively, in other instances, the polymers are effectively composed of two different subunits, in which the percentage of each subunit may vary from less than 1:99 to more than 99:1, or alternatively 10:90, 15:85, 25:75, 40:60, 50:50, 60:40, 75:25, 85:15, 90:10 or the like. For example, in some instances, a polymer may be composed of two different subunits that may be both represented by the generic formula **2** and **3**, but which differ in their chemical identity. In certain embodiments, the polymers may have just a few percent, or even less (for example, about 5, 2.5, 1, 0.5, 0.1%) of the subunits having phosphorous-based linkages. In other embodiments, in which three or more different monomeric units are present, the present invention contemplates a range of mixtures like those taught for the two-component systems.

In yet another aspect, the instant invention relates to compounds having the structure **4**:



4

wherein:

Y represents independently for each occurrence alkoxy, -OH, sulfonate, sulfate,sulfonyl, sulfoxido, -O(aryl), -O(acyl), -O(sulfonyl), trifluoro-methanesulfonyl, or methanesulfonyl.

R_1 is absent or present 1, 2, or 3 times;

R_2 is absent or present 1, 2, or 3 times;

Z represents optionally substituted alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

R_1 and R_2 represent independently for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

m is an integer in the range 0 to 8 inclusive; and salts thereof.

Some disclosed compounds have in common esters of and between coumaric acid and zosteric acid. Zosteric acid has previously been shown to participate directly in bioadhesive control mechanisms. However, more recent analyses suggest esters of coumaric acid and mixed esters of coumaric acid and zosteric acid have substantially greater activity in bioadhesive control mechanisms than zosteric acid alone.

Compounds of the invention have been shown to provide one or more plant and animal lectin-like activities. Lectins bind to cell surface proteoglycans, which function in the attachment of pathogens such as viruses and bacteria. Accordingly the lectin-like

activities of compounds of the invention are useful in treating and preventing infections and other receptor-mediated diseases and conditions.

The ability of the compounds to bind to certain cell surface sites is useful for agonizing or antagonizing certain cell surface interactions which are otherwise affected by animal or plant lectin proteins. The extracellular polysaccharides produced by fouling organisms are often highly sulfated, and these sulfate esters play an important role in polymerization (e.g. glue/gel formation).

The instant invention is based, at least in part, on the finding that some compounds of the invention inhibit attachment of parasitic fungi spores to plants, as well as hyphal production from previously attached spores. Even after prolonged exposure, the presence of the compounds of the invention on the plants did not result in any toxic or growth inhibitory effect.

In addition, greenhouse studies revealed that the compound effectively controlled the disease on plants exposure to abnormal high spore pressures. Again, no detectable phytotoxicity was observed. In evaluations assessing fungal spore attachment on man-made surfaces, it was determined that a compound of the invention provided nearly 100% inhibition of attachment of two species of fungal pathogens. If fungal spores were allowed to attach, the compound provided 100% inhibition of spore germination.

By blocking spore attachment, an initial step in the infection process, the compounds of the invention may provide a highly effective antifungal and antibacterial agent. In addition, since essentially all fungal plant pathogens use spores to recognize the host plant, attach, germinate, penetrate the host plant tissue and proliferate hyphae that allows the fungus access to the plant's nutrients for growth and reproduction, the compounds are broad-based antifungal agents. In addition a series of investigations on several species of bacteria, microalgae, macroalgal spores and invertebrates has confirmed that the inhibitory mode-of-action is through a non-toxic means (Zimmerman et al., (1995) US Patent 5,384,176; Zimmerman et al., (1997) US Patent 5,607,741; Todd et al., *Phytochemistry 34:* 401-404 (1993); Sundberg et al., *Naval Research Reviews* (1997) 4: 51-59).

One of skill in the art will recognize that a compound of the invention can be varied as required to optimize the overall chemical properties of the particular compound for specific uses, while retaining the antifouling (AF) activity. For example, the length of an

alkyl chain can be extended or shortened to control the rate of dissolution of the compound from a structure or a coating. Alternatively, additional functional groups can be added to the alkyl chain to further vary the chemical nature of the molecule.

Implantable medical devices, using artificial materials alone or in combination with naturally-derived materials, can be treated with compounds either by surface coating or by incorporation. Metals may be suitably treated with surface coats while retaining their biological properties. In certain embodiments of the present invention, metals may be treated with paints or with adherent layers of polymers or ceramics that incorporate the compounds of the invention. Certain embodiments treated in this manner may be suitable for orthopedic applications, for example, pins, screws, plates or parts of artificial joints. Methods for surface treatment of metals for biological use are well-known in the relevant arts. Other materials besides metals can be treated with surface coats of compounds according to the present invention as the medical application requires.

Implantable devices may comprise materials suitable for the incorporation of the instant compounds. Embodiments whose components incorporate compounds of the invention can include polymers, ceramics and other substances. Materials fabricated from artificial materials may also be resorped when they are placed in the body. Such materials can be called bioabsorbable. As an example, polyglycolic acid polymers can be used to fabricate sutures and orthopedic devices. Those of ordinary skill in the art will be familiar with techniques for incorporating agents into the polymers used to shape formed articles for medical applications. AF agents can also be incorporated into glues, cements or adhesives, or in other materials used to fix structures within the body or to adhere implants to a body structure. Examples include polymethylmethacrylate and related compounds, used for the affixation of orthopedic and dental prostheses within the body. The presence of the compounds of the instant invention can decrease biofilm formation in those structures in contact with the glue, cement, or adhesive. Alternatively, a compound of the invention can coat or can permeate the formed article. In these compositions, the formed article allows diffusion of the compound, or functional portion thereof, into the surrounding environment, thereby preventing fouling of the appliance itself. Microcapsules bearing compounds can also be imbedded in the material. Materials incorporating compounds are adaptable to the manufacture of a wide range of medical devices, some of which are disclosed below. Other examples will be readily apparent to those practitioners of ordinary skill in the art.

In one embodiment, compounds of the invention can be applied to or incorporated in certain medical devices that are intended to be left in position permanently to replace or restore vital functions. As one example, ventriculoatrial or ventriculoperitoneal shunts are devised to prevent cerebrospinal fluid from collecting in the brain of patients whose normal drainage channels are impaired. As long as the shunt functions, fluid is prevented from accumulating in the brain and normal brain function can continue. If the shunt ceases to function, fluid accumulates and compresses the brain, a complication. If the shunt becomes infected, it causes an infection to enter the central portions of the brain, another life-threatening complication. These shunts commonly include a silicone elastomer or another polymer as part of their fabrication. Silicones are understood to be especially suited for combination with compounds according to the present invention.

Another shunt that has life-saving import is a dialysis shunt, a piece of polymeric tubing connecting an artery and a vein in the forearm to provide a kidney failure patient a means by which the dialysis equipment can cleanse the bloodstream. Even though this is a high-flow conduit, it is susceptible to the formation of biofilms and subsequent infection. If a shunt becomes infected, it requires removal and replacement. Since dialysis may be a lifelong process, and since there are a limited number of sites where shunts can be applied, it is desirable to avoid having to remove one due to infectious complications. Imbedding or otherwise contacting the compounds of the invention with the shunt material can have this desired effect.

Heart valves comprising artificial material are understood to be vulnerable to the dangerous complication of prosthetic valve endocarditis. Once established, it carries a mortality rate as high as 70%. Biofilms are integrally involved in the development of this condition. At present, the only treatment for established contamination is high-dose antibiotic therapy and surgical removal of the device. The contaminated valve must be immediately replaced, since the heart cannot function without it. Because the new valve is being inserted in a recently contaminated area, it is common for prosthetic valve endocarditis to affect the replacement valve as well. Artificial heart valves comprised of the compounds of the invention may reduce the incidence of primary and recurrent prosthetic valve endocarditis. Compounds of the invention can be applied to the synthetic portions or the naturally-derived portions of heart valves.

Pacemakers and artificial implantable defibrillators commonly comprise metallic parts in combination with other synthetic materials. These devices, which may be coated with a polymeric substance such as silicone are typically implanted in subcutaneous or intramuscular locations with wires or other electrical devices extending intrathoracically or intravascularly. If the device becomes colonized with microorganisms and infected, it must be removed. A new device can be replaced in a different location, although there are a finite number of appropriate implantation sites on the body. Devices comprising the compounds of the invention may inhibit contamination and infection, or substantially reduce the risk thereof.

Devices implanted into the body either temporarily or permanently to pump pharmacological agents into the body can comprise metallic parts in combination with other synthetic materials. Such devices, termed infusion pumps, can be entirely implanted or can be partially implanted. The device may be partially or entirely covered with a polymeric substance, and may comprise other polymers used as conduits or tubes. Incorporating AF agents according to the present invention into the coating materials imposed upon these devices or into the materials used for the devices themselves, their conduits or their tubing may inhibit their contamination and infection.

Equally lifesaving are the various vascular grafting prostheses and stents intended to bypass blocked arteries or substitute for damaged arteries. Vascular grafting prostheses, made of Teflon, dacron, Gore-tex®, expanded polytetrafluoroethylene (e-PTFE), and related materials, are available for use on any major blood vessel in the body. Commonly, for example, vascular grafting prostheses are used to bypass vessels in the leg and are used to substitute for a damaged aorta. They are put in place by being sewn into the end or the side of a normal blood vessel upstream and downstream of the area to be bypassed or replaced, so that blood flows from a normal area into the vascular grafting prosthesis to be delivered to other normal blood vessels. Stents comprising metallic frames covered with vascular grafting prosthesis fabric are also available for endovascular application, to repair damaged blood vessels.

When a vascular grafting prosthesis becomes infected, it can spread infection through the entire bloodstream. Furthermore, the infection can weaken the attachment of the vascular grafting prosthesis to the normal blood vessel upstream or downstream, so that blood can leak out of it. If the attachment ruptures, there can be life-threatening

hemorrhage. When a vascular grafting prosthesis becomes infected, it needs to be removed. It is especially dangerous to put another vascular grafting prosthesis in the same spot because of the risk of another infection, but there are often few other options. Vascular grafting prostheses comprising compounds of the invention can resist infections, thereby avoiding these devastating complications.

Vascular grafting prostheses of small caliber are particularly prone to clotting. A vascular grafting prosthesis comprising a compound of the invention may not only prevent biofilm formation , but also inhibit clotting as described above, allowing a smaller diameter vascular grafting prosthesis to be more reliable. A common site for clotting is the junction point between the vascular grafting prosthesis and the normal vessel, called the anastomosis. Even if an artificial vascular grafting prosthesis is not used, anywhere that two vessels are joined or anywhere there is a suture line that penetrates a natural blood vessel, there is a potential for clotting to take place. A clot in a vessel can occlude the vessel entirely or only partially; in the latter case, blood clots can be swept downstream, damaging local tissues. Using suture comprised of the compounds of the invention may inhibit clotting at these various suture lines. The smaller the vessel, the more likely that a clot forming within it will lead to a total occlusion. This can have disastrous results: if the main vessel feeding a tissue or an organ becomes totally occluded, that structure loses its blood supply and can die. Microsurgery provides dramatic examples of the damage that can occur with anastomotic clotting. In microsurgery, typically only a single tiny vessel is feeding an entire tissue structure like a finger or a muscle. If the vessel clots off, the tissue structure can quickly die. Microsurgery typically involves vessels only one to four millimeters in diameter. It is understood that the sutures penetrating the vessel at the anastomosis are likely sites for clots to form. Microsurgical sutures comprising a compound of the invention would result in localized administration of an anticoagulant at the site most likely to be damaged by clotting.

Suture material used to anchor vascular grafting prostheses to normal blood vessels or to sew vessels or other structures together can also harbor infections. Sutures used for these purposes are commonly made of prolene, nylon or other monofilamentous nonabsorbable materials. An infection that begins at a suture line can extend to involve the vascular grafting prosthesis. Suture materials comprising a compound of the invention would have increased resistance to infection.

A suture comprising a compound of the invention would be useful in other areas besides the vasculature. Wound infections at surgical incisions may arise from microorganisms that lodge in suture materials placed at various levels to close the incision. General surgery uses both nonabsorbable and absorbable sutures. Materials for nonabsorbable sutures include prolene and nylon. Absorbable sutures include materials like treated catgut and polyglycolic acid. Absorbable sutures retain tensile strength for periods of time from days to months and are gradually resorbed by the body. Fabricating an absorbable or a nonabsorbable suture comprising a compound of the invention and which retains the handling and tensile characteristics of the material is within the skill of artisans in the field.

Medical prostheses comprising compounds of the invention would be expected to have reduced contamination and subsequent local infection, thereby obviating or reducing the need to remove the implant with the attendant destruction of local tissues. Destruction of local tissues, especially bones and ligaments, can make the tissue bed less hospitable for supporting a replacement prosthesis. Furthermore, the presence of contaminating microorganisms in surrounding tissues makes recontamination of the replacement prosthesis easily possible. The effects of repeated contamination and infection of structural prosthetics is significant: major reconstructive surgery may be required to rehabilitate the area in the absence of the prosthesis, potentially including free bone transfers or joint fusions. Furthermore, there is no guarantee that these secondary reconstructive efforts will not meet with infectious complications as well. Major disability, with possible extremity amputation, is the outcome from contamination and infection of a structural prosthesis.

Tissue expanders are sacs made of silicone elastomers adapted for gradual filling with a saline solution, whereby the filling process stretches the overlying tissues to generate an increased area of tissue that can be used for other reconstructive applications. Tissue expanders can be used, for example, to expand chest wall skin and muscle after mastectomy as a step towards breast reconstruction. Tissue expanders can also be used in reconstructing areas of significant skin loss in burn victims. A tissue expander is usually intended for temporary use: once the overlying tissues are adequately expanded, they are stretched to cover their intended defect. If a tissue expander is removed before the expanded tissues are transposed, though, all the expansion gained over time is lost and the tissues return nearly to their pre-expansion state. The most common reason for premature tissue expander removal

is infection. These devices are subjected to repeated inflations of saline solution, introduced percutaneously into remote filling devices that communicate with the expander itself. Bacterial contamination of the device is thought to occur usually from the percutaneous inflation process. Once contamination is established and a biofilm forms, local infection is likely. Expander removal, with the annulment of the reconstructive effort, is needed to control the infection. A delay of a number of months is usually recommended before a new tissue expander can be inserted in the affected area. The silicone elastomer used for these devices is especially suitable for integrating with sulfate ester AF agents. Use of these agents in the manufacture of these articles may reduce the incidence of bacterial contamination, biofilm development and subsequent local infection.

Insertable devices include those objects made from synthetic materials applied to the body or partially inserted into the body through a natural or an artificial site of entry. Examples of articles applied to the body include contact lenses and stoma appliances. An artificial larynx is understood to be an insertable device in that it exists in the airway, partially exposed to the environment and partially affixed to the surrounding tissues. An endotracheal or tracheal tube, a gastrostomy tube or a catheter are examples of insertable devices partially existing within the body and partially exposed to the external environment. The endotracheal tube is passed through an existing natural orifice. The tracheal tube is passed through an artificially created orifice. Under any of these circumstances, the formation of biofilm on the device permits the ingress of microorganisms along the device from a more external anatomic area to a more internal anatomic area. The ascent of microorganisms to the more internal anatomic area commonly causes local and systemic infections.

As an example, biofilm formation on soft contact lenses is understood to be a risk factor for contact-lens associated corneal infection. The eye itself is vulnerable to infections due to biofilm production. Incorporating an antifouling agent in the contact lens itself and in the contact lens case can reduce the formation of biofilms, thereby reducing risk of infection. Sulfate ester AF agents can also be incorporated in ophthalmic preparations that are periodically instilled in the eye.

As another example, biofilms are understood to be responsible for infections originating in tympanostomy tubes and in artificial larynxes. Biofilms further reside in tracheostomy tubes and in endotracheal tubes, permitting the incursion of pathogenic

bacteria into the relatively sterile distal airways of the lung. These devices are adaptable to the incorporation or the topical application of sulfate ester AF agents to reduce biofilm formation and subsequent infectious complications.

As another example, a wide range of vascular catheters are fabricated for vascular access. Temporary intravenous catheters are placed distally, while central venous catheters are placed in the more proximal large veins. Catheter systems can include those installed percutaneously whose hubs are external to the body, and those whose access ports are buried beneath the skin. Examples of long-term central venous catheters include Hickman catheters and Port-a-caths. Catheters permit the infusion of fluids, nutrients and medications; they further can permit the withdrawal of blood for diagnostic studies or the transfusion of blood or blood products. They are prone to biofilm formation, increasingly so as they reside longer within a particular vein. Biofilm formation in a vascular access device can lead to the development of a blood-borne infection as planktonic organisms disseminate from the biofilm into the surrounding bloodstream. Further, biofilm formation can contribute to the occlusion of the device itself, rendering it non-functional. If the catheter is infected, or if the obstruction within it cannot be cleared, the catheter must be removed. Commonly, patients with these devices are afflicted with serious medical conditions. These patients are thus poorly able to tolerate the removal and replacement of the device. Furthermore, there are only a limited number of vascular access sites. A patient with repeated catheter placements can run out of locations where a new catheter can be easily and safely placed. Incorporation of sulfate ester AF agents within catheter materials or application of these agents to catheter materials can reduce fouling and biofilm formation, thereby contributing to prolonged patency of the devices and minimizing the risk of infectious complications.

As another example, a biliary drainage tube is used to drain bile from the biliary tree to the body's exterior if the normal biliary system is blocked or is recovering from a surgical manipulation. Drainage tubes can be made of plastics or other polymers. A biliary stent, commonly fabricated of a plastic material, can be inserted within a channel of the biliary tree to keep the duct open so that bile can pass through it. Biliary sludge which forms as a result of bacterial adherence and biofilm formation in the biliary system is a recognized cause of blockage of biliary stents. Pancreatic stents, placed to hold the pancreatic ducts open or to drain a pseudocyst of the pancreas, can also become blocked with sludge.

Biofilms are furthermore implicated in the ascent of infections into the biliary tree along a biliary drainage tube. Ascending infections in the biliary tree can result in the dangerous infectious condition called cholangitis. Incorporation of compounds of the invention in the materials used to form biliary drainage tubes and biliary stents can reduce the formation of biofilms, thereby decreasing risk of occlusions and infections.

As another example, a peritoneal dialysis catheter is used to remove bodily wastes in patients with renal failure by using fluids instilled into and then removed from the peritoneal cavity. This form of dialysis is an alternative to hemodialysis for certain renal failure patients. Biofilm formation on the surfaces of the peritoneal dialysis catheter can contribute to blockage and infection. An infection entering the peritoneal cavity is termed a peritonitis, an especially dangerous type of infection. Peritoneal dialysis catheters, generally made of polymeric materials like polyethylene, can be coated with or impregnated with sulfate ester AF agents to reduce the formation of biofilms.

As yet another example, a wide range of urological catheters exist to provide drainage of the urinary system. These catheters can either enter the natural orifice of the urethra to drain the bladder, or they can be adapted for penetration of the urinary system through an iatrogenically created insertion site. Nephrostomy tubes and suprapubic tubes represent examples of the latter. Catheters can be positioned in the ureters on a semipermanent basis to hold the ureter open; such a catheter is called a ureteral stent. Urological catheters can be made from a variety of polymeric products. Latex and rubber tubes have been used, as have silicones. All catheters are susceptible to biofilm formation. This leads to the problem of ascending urinary tract infections, where the biofilm can spread proximally, carrying pathogenic organisms, or where the sessile organisms resident in the biofilm can propagate planktonic organisms that are capable of tissue and bloodstream invasion. Organisms in the urinary tract are commonly Gram-negative bacteria capable of producing life-threatening bloodstream infections if they spread systemically. Infections wherein these organisms are restricted to the urinary tract can nonetheless be dangerous, accompanied by pain and high fever. Urinary tract infections can lead to kidney infections, called pyelonephritis, that can jeopardize the function of the kidney. Incorporating sulfate ester AF agents can inhibit biofilm formation and may reduce the likelihood of these infectious complications.

A further complication encountered in urological catheters is encrustation, a process by which inorganic compounds comprising calcium, magnesium and phosphorous are deposited within the catheter lumen, thereby blocking it. These inorganic compounds are understood to arise from the actions of certain bacteria resident in biofilms on catheter surfaces. Reducing biofilm formation by the action of sulfate ester AF agents may contribute to reducing encrustation and subsequent blockage of urological catheters.

Other catheter-like devices exist that can be treated with AF agents. For example, surgical drains, chest tubes, hemovacs and the like can be advantageously treated with materials to impair biofilm formation. Other examples of such devices will be familiar to practitioners in these arts.

Materials applied to the body can advantageously employ the AF compounds disclosed herein. Dressing materials can themselves incorporate the AF compounds, as in a film or sheet to be applied directly to a skin surface. Additionally, AF compounds of the instant invention can be incorporated in the glue or adhesive used to stick the dressing materials or appliance to the skin. Stoma adhesive or medical-grade glue may, for example, be formulated to include an AF agent appropriate to the particular medical setting. Stoma adhesive is used to adhere stoma bags and similar appliances to the skin without traumatizing the skin excessively. The presence of infectious organisms in these appliances and on the surrounding skin makes these devices particularly appropriate for coating with AF agents, or for incorporating AF agents therein. Other affixation devices can be similarly treated. Bandages, adhesive tapes and clear plastic adherent sheets are further examples where the incorporation of an AF agent in the glue or other adhesive used to affix the object, or incorporation of an AF agent as a component of the object itself, may be beneficial in reducing skin irritation and infection.

These above examples are offered to illustrate the multiplicity of applications of compounds of the invention in medical devices. Other examples will be readily envisioned by skilled artisans in these fields. The scope of the present invention is intended to encompass all those surfaces where the presence of fouling has adverse health-related consequences. The examples given above represent embodiments where the technologies of the present invention are understood to be applicable. Other embodiments will be apparent to practitioners of these and related arts. Embodiments of the present invention can be compatible for combination with currently employed antiseptic regimens to enhance

their antimicrobial efficacy or cost-effective use. Selection of an appropriate vehicle for bearing a compound of the invention will be determined by the characteristics of the particular medical use. Other examples of applications in medical environments to promote antisepsis will be readily envisioned by those of ordinary skill in the relevant arts.

Antifouling coating compositions of the present invention can also contain a paint base such as vinyl, acrylic, and alkyd resin bases. They can also contain a pigment such as titanium dioxide, a thickener such as bentonite, fillers such as aluminum silicate and calcium silicate, and driers such as cobalt naphthenate and manganese naphthenate. They may also contain solvents or thinners such as mineral spirits, naphtha, benzene, toluene, methylethyl ketone, and the like.

One of skill in the art can synthesize the compounds described above by standard chemical syntheses. The synthesis of certain compounds described herein is via the scheme Z-OH in the presence of SO_2Cl_2 and pyrimidine at –78 C in ethanol to give Z-O-SO_2Cl. One of skill in the art will also recognize that the compositions of the invention can be varied as required to optimize the overall chemical properties of the particular compound for specific uses, while retaining the AF activity. For example, the length of an alkyl chain can be extended or shortened to control the rate of dissolution of the compound from a structure or a coating. Alternatively, additional functional groups can be added to the alkyl chain to further vary the chemical nature of the molecule.

Combinatorial Libraries

The subject methods and compounds readily lend themselves to the creation of combinatorial libraries of compounds for the screening of pharmaceutical, agrochemical or other biological or medically-related activity or material-related qualities. A combinatorial library for the purposes of the present invention is a mixture of chemically related compounds which may be screened together for a desired property; said libraries may be in solution or covalently linked to a solid support. The preparation of many related compounds in a single reaction greatly reduces and simplifies the number of screening processes which need to be carried out. Screening for the appropriate biological, pharmaceutical, agrochemical or physical property may be done by conventional methods.

Diversity in a library may be created at a variety of different levels. For instance, the substrate aryl groups used in a combinatorial approach can be diverse in terms of the core

aryl moiety, e.g., a variegation in terms of the ring structure, and/or can be varied with respect to the other substituents.

A variety of techniques are available in the art for generating combinatorial libraries of small organic molecules. See, for example, Blondelle et al. (1995) Trends Anal. Chem. 14:83; the Affymax U.S. Patents 5,359,115 and 5,362,899: the Ellman U.S. Patent 5,288,514: the Still et al. PCT publication WO 94/08051; Chen et al. (1994) JACS 116:2661: Kerr et al. (1993) JACS 115:252; PCT publications WO92/10092, WO93/09668 and WO91/07087; and the Lerner et al. PCT publication WO93/20242). Accordingly, a variety of libraries on the order of about 16 to 1,000,000 or more diversomers can be synthesized and screened for a particular activity or property.

In an exemplary embodiment, a library of substituted diversomers can be synthesized using the subject reactions adapted to the techniques described in the Still et al. PCT publication WO 94/08051, e.g., being linked to a polymer bead by a hydrolyzable or photolyzable group, e.g., located at one of the positions of substrate. According to the Still et al. technique, the library is synthesized on a set of beads, each bead including a set of tags identifying the particular diversomer on that bead. In one embodiment, which is particularly suitable for discovering enzyme inhibitors, the beads can be dispersed on the surface of a permeable membrane, and the diversomers released from the beads by lysis of the bead linker. The diversomer from each bead will diffuse across the membrane to an assay zone, where it will interact with an enzyme assay. Detailed descriptions of a number of combinatorial methodologies are provided below.

A. Direct Characterization

A growing trend in the field of combinatorial chemistry is to exploit the sensitivity of techniques such as mass spectrometry (MS), e.g., which can be used to characterize sub-femtomolar amounts of a compound, and to directly determine the chemical constitution of a compound selected from a combinatorial library. For instance, where the library is provided on an insoluble support matrix, discrete populations of compounds can be first released from the support and characterized by MS. In other embodiments, as part of the MS sample preparation technique, such MS techniques as MALDI can be used to release a compound from the matrix, particularly where a labile bond is used originally to tether the

compound to the matrix. For instance, a bead selected from a library can be irradiated in a MALDI step in order to release the diversomer from the matrix, and ionize the diversomer for MS analysis.

B) Multipin Synthesis

The libraries of the subject method can take the multipin library format. Briefly, Geysen and co-workers (Geysen et al. (1984) PNAS 81:3998-4002) introduced a method for generating compound libraries by a parallel synthesis on polyacrylic acid-grated polyethylene pins arrayed in the microtitre plate format. The Geysen technique can be used to synthesize and screen thousands of compounds per week using the multipin method, and the tethered compounds may be reused in many assays. Appropriate linker moieties can also been appended to the pins so that the compounds may be cleaved from the supports after synthesis for assessment of purity and further evaluation (c.f., Bray et al. (1990) Tetrahedron Lett 31:5811-5814; Valerio et al. (1991) Anal Biochem 197:168-177; Bray et al. (1991) Tetrahedron Lett 32:6163-6166).

C) Divide-Couple-Recombine

In yet another embodiment, a variegated library of compounds can be provided on a set of beads utilizing the strategy of divide-couple-recombine (see, e.g., Houghten (1985) PNAS 82:5131-5135; and U.S. Patents 4,631,211; 5,440,016; 5,480,971). Briefly, as the name implies, at each synthesis step where degeneracy is introduced into the library, the beads are divided into separate groups equal to the number of different substituents to be added at a particular position in the library, the different substituents coupled in separate reactions, and the beads recombined into one pool for the next iteration.

In one embodiment, the divide-couple-recombine strategy can be carried out using an analogous approach to the so-called "tea bag" method first developed by Houghten, where compound synthesis occurs on resin sealed inside porous polypropylene bags (Houghten et al. (1986) PNAS 82:5131-5135). Substituents are coupled to the compound-bearing resins by placing the bags in appropriate reaction solutions, while all common steps

such as resin washing and deprotection are performed simultaneously in one reaction vessel. At the end of the synthesis, each bag contains a single compound.

D) Combinatorial Libraries by Light-Directed, Spatially Addressable Parallel Chemical Synthesis

A scheme of combinatorial synthesis in which the identity of a compound is given by its locations on a synthesis substrate is termed a spatially-addressable synthesis. In one embodiment, the combinatorial process is carried out by controlling the addition of a chemical reagent to specific locations on a solid support (Dower et al. (1991) Annu Rep Med Chem 26:271-280; Fodor, S.P.A. (1991) Science 251:767; Pirrung et al. (1992) U.S. Patent No. 5,143,854; Jacobs et al. (1994) Trends Biotechnol 12:19-26). The spatial resolution of photolithography affords miniaturization. This technique can be carried out through the use protection/deprotection reactions with photolabile protecting groups.

The key points of this technology are illustrated in Gallop et al. (1994) J Med Chem 37:1233-1251. A synthesis substrate is prepared for coupling through the covalent attachment of photolabile nitroveratryloxycarbonyl (NVOC) protected amino linkers or other photolabile linkers. Light is used to selectively activate a specified region of the synthesis support for coupling. Removal of the photolabile protecting groups by light (deprotection) results in activation of selected areas. After activation, the first of a set of amino acid analogs, each bearing a photolabile protecting group on the amino terminus, is exposed to the entire surface. Coupling only occurs in regions that were addressed by light in the preceding step. The reaction is stopped, the plates washed, and the substrate is again illuminated through a second mask, activating a different region for reaction with a second protected building block. The pattern of masks and the sequence of reactants define the products and their locations. Since this process utilizes photolithography techniques, the number of compounds that can be synthesized is limited only by the number of synthesis sites that can be addressed with appropriate resolution. The position of each compound is precisely known; hence, its interactions with other molecules can be directly assessed.

In a light-directed chemical synthesis, the products depend on the pattern of illumination and on the order of addition of reactants. By varying the lithographic patterns,

many different sets of test compounds can be synthesized simultaneously; this characteristic leads to the generation of many different masking strategies.

E) Encoded Combinatorial Libraries

In yet another embodiment, the subject method utilizes a compound library provided with an encoded tagging system. A recent improvement in the identification of active compounds from combinatorial libraries employs chemical indexing systems using tags that uniquely encode the reaction steps a given bead has undergone and, by inference, the structure it carries. Conceptually, this approach mimics phage display libraries, where activity derives from expressed peptides, but the structures of the active peptides are deduced from the corresponding genomic DNA sequence. The first encoding of synthetic combinatorial libraries employed DNA as the code. A variety of other forms of encoding have been reported, including encoding with sequenceable bio-oligomers (e.g., oligonucleotides and peptides), and binary encoding with additional non-sequenceable tags.

1) Tagging with sequenceable bio-oligomers

The principle of using oligonucleotides to encode combinatorial synthetic libraries was described in 1992 (Brenner et al. (1992) PNAS 89:5381-5383), and an example of such a library appeared the following year (Needles et al. (1993) PNAS 90:10700-10704). A combinatorial library of nominally 7^7 (= 823,543) peptides composed of all combinations of Arg, Gln, Phe, Lys, Val, D-Val and Thr (three-letter amino acid code), each of which was encoded by a specific dinucleotide (TA, TC, CT, AT, TT, CA and AC, respectively), was prepared by a series of alternating rounds of peptide and oligonucleotide synthesis on solid support. In this work, the amine linking functionality on the bead was specifically differentiated toward peptide or oligonucleotide synthesis by simultaneously preincubating the beads with reagents that generate protected OH groups for oligonucleotide synthesis and protected NH_2 groups for peptide synthesis (here, in a ratio of 1:20). When complete, the tags each consisted of 69-mers, 14 units of which carried the code. The bead-bound library was incubated with a fluorescently labeled antibody, and beads containing bound antibody that fluoresced strongly were harvested by fluorescence-activated cell sorting (FACS). The

DNA tags were amplified by PCR and sequenced, and the predicted peptides were synthesized. Following such techniques, compound libraries can be derived for use in the subject method, where the oligonucleotide sequence of the tag identifies the sequential combinatorial reactions that a particular bead underwent, and therefore provides the identity of the compound on the bead.

The use of oligonucleotide tags permits exquisitely sensitive tag analysis. Even so, the method requires careful choice of orthogonal sets of protecting groups required for alternating co-synthesis of the tag and the library member. Furthermore, the chemical lability of the tag, particularly the phosphate and sugar anomeric linkages, may limit the choice of reagents and conditions that can be employed for the synthesis of non-oligomeric libraries. In some embodiments, the libraries employ linkers permitting selective detachment of the test compound library member for assay.

Peptides have also been employed as tagging molecules for combinatorial libraries. Two exemplary approaches are described in the art, both of which employ branched linkers to solid phase upon which coding and ligand strands are alternately elaborated. In the first approach (Kerr JM et al. (1993) J Am Chem Soc 115:2529-2531), orthogonality in synthesis is achieved by employing acid-labile protection for the coding strand and base-labile protection for the compound strand.

In an alternative approach (Nikolaiev et al. (1993) Pept Res 6:161-170), branched linkers are employed so that the coding unit and the test compound can both be attached to the same functional group on the resin. In one embodiment, a cleavable linker can be placed between the branch point and the bead so that cleavage releases a molecule containing both code and the compound (Ptek et al. (1991) Tetrahedron Lett 32:3891-3894). In another embodiment, the cleavable linker can be placed so that the test compound can be selectively separated from the bead, leaving the code behind. This last construct is particularly valuable because it permits screening of the test compound without potential interference of the coding groups. Examples in the art of independent cleavage and sequencing of peptide library members and their corresponding tags has confirmed that the tags can accurately predict the peptide structure.

2) Non-sequenceable Tagging: Binary Encoding

An alternative form of encoding the test compound library employs a set of non-sequencable electrophoric tagging molecules that are used as a binary code (Ohlmeyer et al. (1993) PNAS 90:10922-10926). Exemplary tags are haloaromatic alkyl ethers that are detectable as their trimethylsilyl ethers at less than femtomolar levels by electron capture gas chromatography (ECGC). Variations in the length of the alkyl chain, as well as the nature and position of the aromatic halide substituents, permit the synthesis of at least 40 such tags, which in principle can encode 2^{40} (e.g., upwards of 10^{12}) different molecules. In the original report (Ohlmeyer et al., supra) the tags were bound to about 1% of the available amine groups of a peptide library via a photocleavable o-nitrobenzyl linker. This approach is convenient when preparing combinatorial libraries of peptide-like or other amine-containing molecules. A more versatile system has, however, been developed that permits encoding of essentially any combinatorial library. Here, the compound would be attached to the solid support via the photocleavable linker and the tag is attached through a catechol ether linker via carbene insertion into the bead matrix (Nestler et al. (1994) J Org Chem 59:4723-4724). This orthogonal attachment strategy permits the selective detachment of library members for assay in solution and subsequent decoding by ECGC after oxidative detachment of the tag sets.

Although several amide-linked libraries in the art employ binary encoding with the electrophoric tags attached to amine groups, attaching these tags directly to the bead matrix provides far greater versatility in the structures that can be prepared in encoded combinatorial libraries. Attached in this way, the tags and their linker are nearly as unreactive as the bead matrix itself. Two binary-encoded combinatorial libraries have been reported where the electrophoric tags are attached directly to the solid phase (Ohlmeyer et al. (1995) PNAS 92:6027-6031) and provide guidance for generating the subject compound library. Both libraries were constructed using an orthogonal attachment strategy in which the library member was linked to the solid support by a photolabile linker and the tags were attached through a linker cleavable only by vigorous oxidation. Because the library members can be repetitively partially photoeluted from the solid support, library members can be utilized in multiple assays. Successive photoelution also permits a very high throughput iterative screening strategy: first, multiple beads are placed in 96-well

microtiter plates; second, compounds are partially detached and transferred to assay plates; third, a metal binding assay identifies the active wells; fourth, the corresponding beads are rearrayed singly into new microtiter plates; fifth, single active compounds are identified; and sixth, the structures are decoded.

Some compounds disclosed herein are part of a combinatorial library. A basis for the design of the combinatorial library will be to generate molecules containing functional groups derived from coumaric acid, zosteric acid, and other classes listed in the Examples linked to a spacer of varying structural lengths or conformations (Figure 1). A subset of the library may contain molecules with a single sulfooxy ester functional group attached to the spacer. Another subset may contain similar coumaric acid substituents. Functional groups may be derived from alcohol building blocks of varying structures (see figure 2) that are subsequently sulfonated to generate the sulfooxy ester moiety of zosteric acid (see figure 4).

Spacers will provide a site of attachment for functional groups as well as a linkage site to solid supports in order to facilitate solid phase synthesis of the combinatorial libraries. An additional functional role of the spacer is to provide varying distances and orientations between the functional groups. It is expected these combinatorial libraries will yield novel molecules that more actively control bioadhesive mechanisms. (See figures 3 & 4).

The first set of combinatorial libraries may be synthesized on solid supports using a cleavable linker (see figure 4). This would allow screening of library compounds to be carried out in solution (see figure 5). However, synthesis of combinatorial libraries in solution may also be carried out.

Combinatorial libraries of these compounds will be screened using a 96-well –based adhesion assay based on fluorescence tagging of bacteria or fungal spores. This screen may also be extended to include other organisms including viruses, yeast and invertebrate larvae. A summary of the screening approach is illustrated in figure 5 (Below). The screening strategy includes both an adhesion and a viability assay in order to identify non-biocidile molecules with adhesion control properties.

Active molecules identified through the above screening methods will then be advanced for further characterization. This will include structural determination, solubility properties, efficacy testing against a broad range of hosts and toxicity evaluations.

EXEMPLIFICATION

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intendend to limit the invention.

Example 1

General Assay Protocol

Compounds were packaged in 2-5 mg quantities in wells A02-D02 of a 96-deep well polypropylene microplate, tightly sealed with a plastic dimpled lid. The compounds were handled under slightly different conditions as they fell into two solubility classes. Compounds A02 and B02, insoluble in water, were dissolved in DMSO and tested at a final concentration of 0.5% with 5% DMSO, a concentration of DMSO that has no effect on any of the organisms used in the assays. Compounds C02 and D02, soluble in water, were dissolved in E-pure water, and tested at 0.5% after having been adjusted to the proper buffer condition for the assay. The compounds were tested in three species, *Staphylococcus epidermidis*, important in human pathology, *Colletotrichum acutatum*, a plant pathogenic fungus, and *Pseudoalteramonas atlantica*, a marine biofouling bacterium. The two bacteria were tested under a 96 well multiwell plate protocol, using the fluorescent dye, Syto 13, to quantitate the assay. The fungus was tested in a 35 mm petri dish protocol using spore counts to quantitate the test.

Example 2

Standard assay for *Staphyloccocus epidermidis*

96 well plate assay: Reagents: 10XPBS ; 80g NaCl 1L; 2g KH_2PO_4;11.35g/21.4g Na_2HPO_4/Na_2HPO_4 $7H_2O$; 2g KCl; pH 7.2 do not pH; SYTO 13 5mM in DMSO Cat # 7575; LB growth media: *S. epidermidis* (ATCC # 12228) is grown on nutrient agar plates from -70°C stock, a single colony should be picked and subcultured in LB media for overnight growth at 37°C shaking 200 rpm. Next day use $1/100^{th}$ volume of overnight culture to start new culture, this culture will need to grow for 4-5 hr which will be early log

phase of growth. Pour culture into 50 mL conical tubes and centrifuge at 3000 rpm for 10 min at R.T., pour off supernatant and gently re-suspend pellet in 0.5 volume of original culture with 1XPBS buffer. Use this re-suspended culture to determine OD using the Shimadzu spectrophotometer and dilute cells to 1 OD at 600nm. Experimental controls and samples need to be added to wells prior to adding cells, positive control at 2%, 1%, and 0. 1% added to three wells each. Dynex 96 well black solid bottom plates are used for the fluorescence assay. Prep standard curve wells by adding 50 uL of 1XPBS in each well, 15 wells are needed for a 1:1 dilution series starting at 0.5 - 0.03125 OD of cells in triplicate. Make dilutions and add the Syto 13 probe (1uM final) fresh just before adding to the wells. The 9 wells below standards need to be saved for background controls, these also will need the probe as well. Working O.D. will be 0.0625 OD and Syto 13 probe is 1uM final, well volume is 100 uL. Once experimental samples have been incubated in the wells for a minimum of 10 min then add cells to each well according to final volume and concentrations. Incubate cells on plate for 25 min then wash on Tecan Plate washer 5 cycles of 300 uL rinse with 1XPBS solution. At last cycle dispense 100 uL of 1 xPBS solution and read fluorescence. Excitation is 488nm and Emission at 509 nm, use the Tecan Microfluor Fluorescein setting.

Example 3

***Pseudoalteromonas atlantica* 96 well plate assay**

Media and reagent preparation: Marine broth (Defico 2216): make the medium according to the manufacture's instruction and autoclave for 20 min. There will be precipitation after cooling. Let sit for 1-2 days and transfer the clear part to a sterile bottle and store at RT. 80% seawater: It can be either filtered natural seawater (FSW) or artificial seawater (ASW, sigma S-9883). Autoclave to sterilize and store at RT PBS: see SOP PHY001 1 uM Syto-13: add 1 ul of 5mM stock (in DMSO) from Molecular Probe (Cat# 7575) to every 5 ml PBS. Preparation for cell material: Start culture in sterile marine broth late afternoon (ca. 5-6 pm) one day before assaying. Grow the culture at 26-29°C in a shaking incubator (200 rpm).

Harvested the cells next morning when the OD600 of the culture reaches 0.7-1.0, using centrifugation (3000rpm, 10min, RT). Resuspend the cells with 80% seawater to OD between 0.3 to 1.0, then use the cell preparation within an hour.

Assaying procedure: Choose a plate for the assay: Dynex total-black plate or Nunc total-black plate (with or without coating). Make solutions containing ZA double concentrated as intended to use, using 80% seawater. Add 50 ul the solutions to each well on the plate. Add just 50 ul 80% seawater to the wells used as control. Then add 50 ul of the cell preparation described above into those wells. Shake the plate briefly to make sure that cells are mixed with ZA solution. Incubate the plate at RT for 40 min (no shaking is needed).

After incubation, wash the plate with the plate-washer using 80% seawater, and then add 100 ul of 1 uM Syto-13 in PBS into each well. Incubate the plate with the dye solution for 15 min in darkness or at least under dim light. Read the plate with Tecan using the program "Syto-13" (Excitation is 488nm and Emission at 509 nm). Set the gain at either 100 or optimal.

Example 4

***Colletotrichum acutatum* petri dish assay**

Reagents: Tap water 50/50 Oatmeal/PDA agar plates. *C. acutatum* is grown on 50/50 oatmeal PDA agar plates for 6-8 days. Seven days are optimal. Flood plate with 10-15 ml tap water, pipetting wash gently over the culture to tease the spores loose. Transfer wash into 15 or 50 ml conical tubes and centrifuge at 3000 rpm for 5 min at R.T., pour off supernatant and vortex pellet in 10 ml of tap water to resuspend pellet. Count spores at a 1:100 dilution, using a haemocytometer. Counts generally are 6-8 $X10^7$ spores/ml. Dilute spores to $2X10^5$ spores/ml; about 35 µl/ 10 ml tap water. Refrigerate spore suspensions. For experiment, data points are staggered at 15 min intervals. Set up three eppendorf tubes. Add 100 µl of test compound made up in e-pure water to the tube. Add 100 µl of spore suspension to the tubes. Allow to equilibrate for 15 min. Transfer 100 µl from each tube to a 35 mm Falcon petri dish which has been labeled and marked with a graphic on the bottom to orient the plate. Place the drop in the center of a graphic.

At 55 minutes take 5 images of the spores on the surface of the petri dish. At 1 hr after the spores were originally put into the eppendorf tubes, wash spores from petri dish by adding three ml of e-pure water to each dish and vortex dishes on the microplate shaker at a setting of 900 rpm for 30 seconds. Take an additional 5 images per dish following the same pattern as in other step. There should be ~200-500 spores/field. Count the spores in the images using the Image Pro software,

enter the counts into the Excel template set up for this assay, which also calculates the % inhibition for each experimental point.

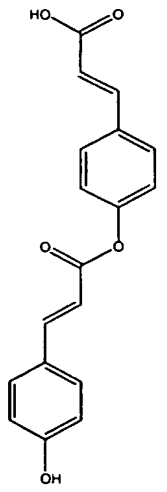
Example 5

Percent Inhibition of Adhesion of Cells or Spores to Polystyrene Surfaces

	Staphylococcus epidermidis	*Pseudoalteramonas atlantica*	*Colletotrichum acutatum*
Compound A02	22%	ND*	-12%
Compound B02	ND	ND	-16%
Compound C02	6%	ND	-36%
Compound D02	74%	32%	-19%

* ND, not determinable in assay

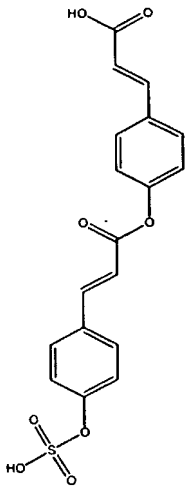
Compound D02 showed sufficient anti-adhesive activity in the *Staphyloccocus* assay to qualify for follow-up in a two-rate screen.



$C_{18}H_{14}O_5$
Exact Mass: 310.08
Mol. Wt.: 310.30
C, 69.67; H, 4.55; O, 25.78
3-{4-[3-(4-Hydroxy-phenyl)-acryloyloxy]-phenyl}-acrylic acid

Example 6

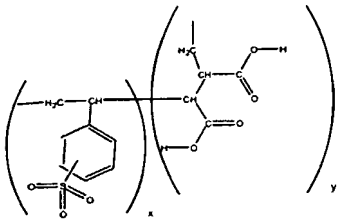
Example 7



$C_{18}H_{14}O_8S$
Exact Mass: 390.04
Mol. Wt.: 390.36
C, 55.38; H, 3.61; O, 32.79; S, 8.21
3-{4-[3-(4-Sulfooxy-phenyl)-acryloyloxy]-phenyl}-acrylic acid

Example 8

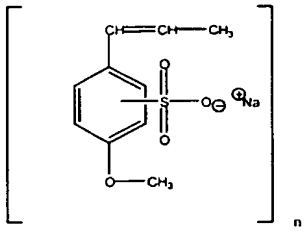
Poly(styrenesulfonic acid-co-maleic acid)sodium salt



Pseudoalteromonas atlantica	Staphylococcus epidermidis	Colletotrichum acutatum
+	+/-	-

Example 9

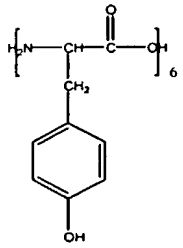
Polyanetholesulfonic acid



Pseudoalteromonas atlantica	Staphylococcus epidermidis	Colletotrichum acutatum
+	+	-

Example 10

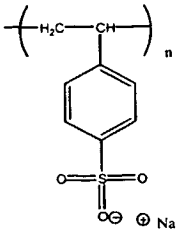
l-Tyrosine hexamer



Pseudoalteromonas atlantica	Staphylococcus epidermidis	Colletotrichum acutatum
NT	NT	+

Example 11

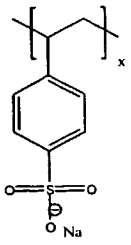
Poly(sodium 4-styrenesulfonate



Pseudoalteromonas atlantica	Staphylococcus epidermidis	Colletotrichum acutatum
+	+	-

Example 12

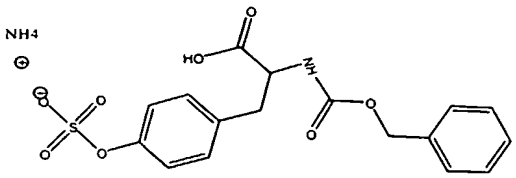
Poly(styrene sulfonate)



# units (x)	Pseudoalteromonas atlantica	Staphylococcus epidermidis	Colletotrichum acutatum
8	+	-	NT
24	+	-	NT
38	+	-	NT
77	+	+	NT

Example 13

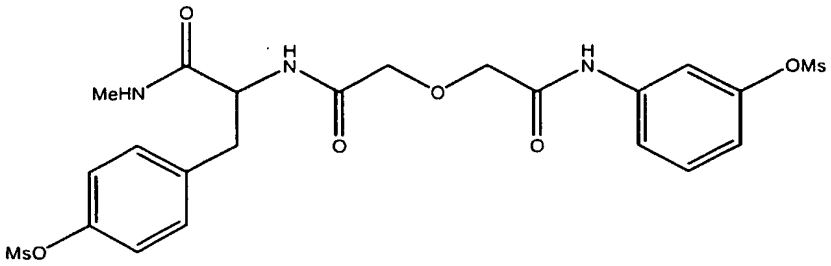
Sulfated Cbz-Tyrosine



Pseudoalteromonas atlantica	Staphylococcus epidermidis	Colletotrichum acutatum
+	+	-

Example 14

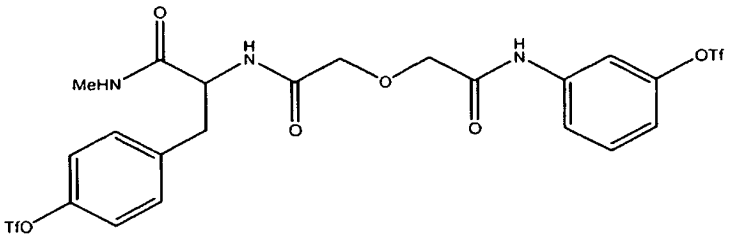
AO2



Methanesulfonic acid
4-(2-{2-[(3-methanesulfonyloxy-phenylcarbamoyl)-methoxy]-acetylamino}-2-methylcarbamoyl-ethyl)-phenyl ester

Example 15

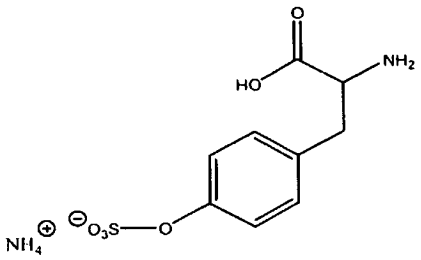
BO2



Trifluoro-methanesulfonic acid 4-(2-methylcarbamoyl-2-{2-[(3-trifluoromethanesulfonyloxy-phenylcarbamoyl)-methoxy]-acetylamino}-ethyl)-phenyl ester

Example 16

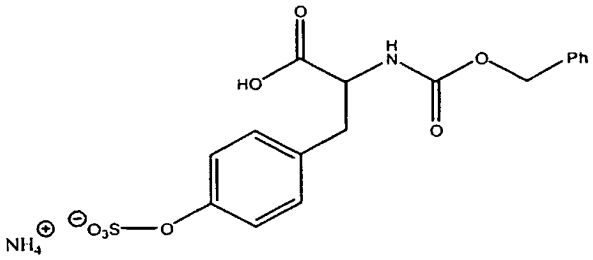
CO2



Sulfated Tyrosine

Example 17

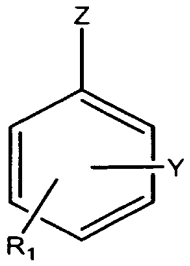
DO2



Sulfated Cbz-Tyrosine

Claims:

1. The anti- adhesive compounds having a structure **1**:



1

wherein:

Y represents alkoxy, -OH, sulfonate, sulfate, sulfonyl, sulfoxido, -O-(aryl), -O-(acyl),
-O-(sulfonyl), trifluoro-methanesulfonyl, or methanesulfonyl;

R_1 is absent or present 1, 2, or 3 times;

Z represents alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

R_1 represents for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

m is an integer in the range 0 to 8 inclusive; and salts thereof.

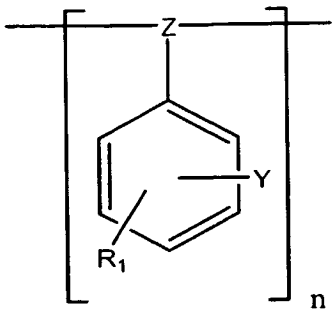
2. The compound of claim 1, wherein Y represents sulfonate, sulfate, sulfonyl, sulfoxido, trifluoro-methanesulfonyl, or methanesulfonyl.

3. The compound of claim 1, wherein R_1 is absent.

4. The compound of claim 3 wherein Z represents alkyl or alkenyl.

5. The compound of claim 4, wherein Y represents sulfonate, sulfate, sulfonyl, sulfoxido, trifluoro-methanesulfonyl, or methanesulfonyl.

6. An anti-adhesive polymeric compound comprising a monomeric unit having a structure 2:



2

wherein:

Y represents alkoxy, -OH, sulfonate, sulfate,sulfonyl, sulfoxido, -O-(aryl), -O-(acyl), -O-(sulfonyl), trifluoro-methanesulfonyl, or methanesulfonyl;

R_1 is absent or present 1, 2, or 3 times;

Z represents optionally substituted alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

R_1 represents for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

m is an integer in the range 0 to 8 inclusive;

n is an integer from 2 to about 1000; and the salts thereof.

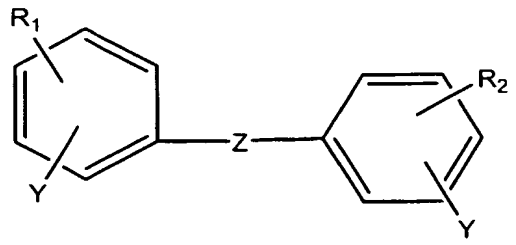
7. The anti-adhesive polymer compound of claim 6 wherein Y represents sulfonate, sulfate, sulfonyl, sulfoxido, trifluoro-methanesulfonyl, or methanesulfonyl.

8. The anti-adhesive polymer compound of claim 7 wherein R_1 is absent.

9. The anti-adhesive polymer compound of claim 7 wherein Z represents alkyl or alkenyl.

10. The anti-adhesive polymer compound of claim 6 further comprising monomeric units comprising a divalent organic group.

11. The anti-adhesive compounds having a structure **4**:



4

wherein:

Y represents alkoxy, -OH, sulfonate, sulfate, sulfonyl, sulfoxido, -O(aryl), -O(acyl), -O-(sulfonyl), trifluoro-methanesulfonyl, or methanesulfonyl.

R_1 is absent or present 1,2, or 3 times;

R_2 is absent or present 1,2, or 3 times;

Z represents optionally substituted alkyl, alkenyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or $-(CH_2)_m-R_{80}$;

R_{80} represents independently for each occurrence aryl, cycloalkyl, cycloalkenyl, heterocyclyl, or polycyclyl;

R_1 and R_2 represent independently for each occurrence alkyl, alkynyl, alkynyl, halogen, formyl, acyl, carboxylate, alkoxycarbonyl, aryloxycarbonyl, carboxamido, alkylamino, acylamino, hydroxyl, alkoxyl, acyloxy, hydroxyalkyl, alkoxyalkyl, aminoalkyl, (alkylamino)alkyl, thio, alkylthio, thioalkyl, (alkylthio)alkyl, carbamoyl, urea, thiourea, sulfonyl, sulfonate, sulfonamido, sulfonylamino, or sulfonyloxy; and

m is an integer in the range 0 to 8 inclusive; and salts thereof.

12. The compound of claim 11, wherein Y represents sulfonate, sulfate, sulfonyl, sulfoxido, trifluoro-methanesulfonyl, or methanesulfonyl.

13. The compounds 3-{4-[3-(4-Hydroxy-phenyl)-acryloyloxy]-phenyl}-acrylic acid, 3-{4-[3-(4-Sulfooxy-phenyl)-acryloyloxy]-phenyl}-acrylic acid and sulfated Cbz-Tyrosine.

14. The compounds Poly(styrenesulfonic acid-co-maleic acid)sodium salt; Polyanetholesulfonic acid; l-Tyrosine hexamer, Poly(sodium 4-styrenesulfonate), and Poly(styrene sulfonate).

15. The compounds methanesulfonic acid 4-(2-{2-[(3-methansulfonyloxy-phenylcarbamoyl)-methoxy]-acetylamino}-2-methylcarbamoyl-ethyl)-phenyl ester; trifluoro-methanesulfonic acid 4-(2-methylcarbamoyl-2-{2-[(3-trifluoromethanesulfonyloxy-phenylcarbamoyl)-methoxy]-acetylamino}-ethyl)-phenyl ester; and sulfated tyrosine.

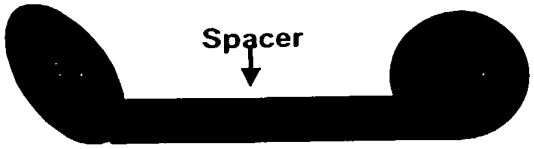


FIGURE 1

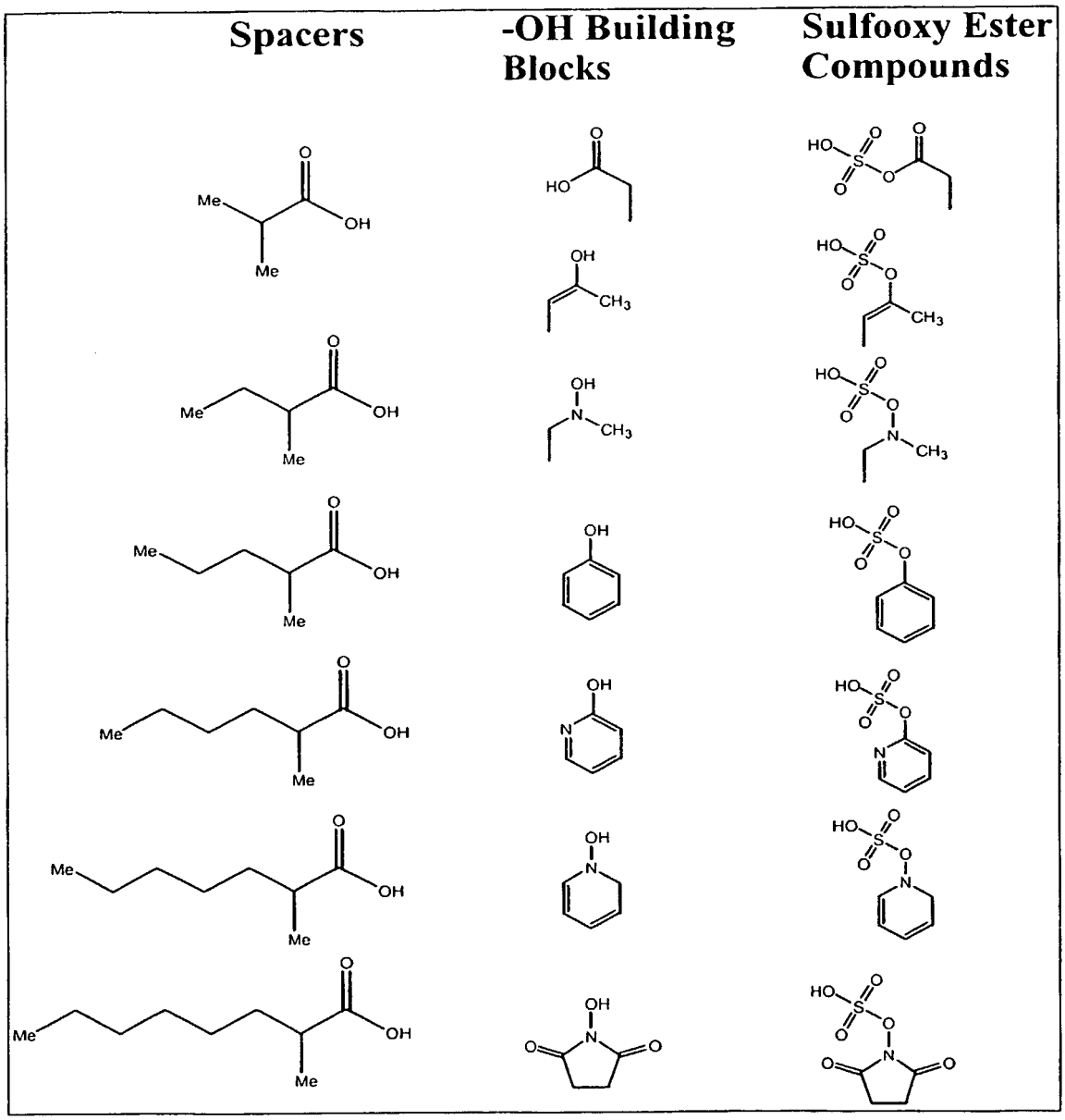


FIGURE 2

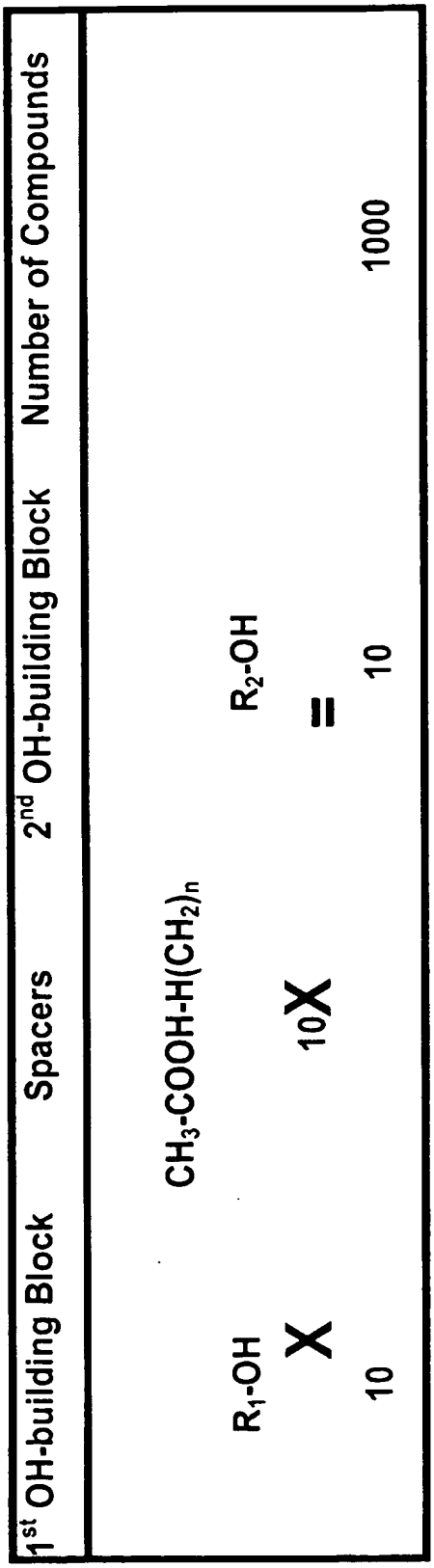


FIGURE 3A.

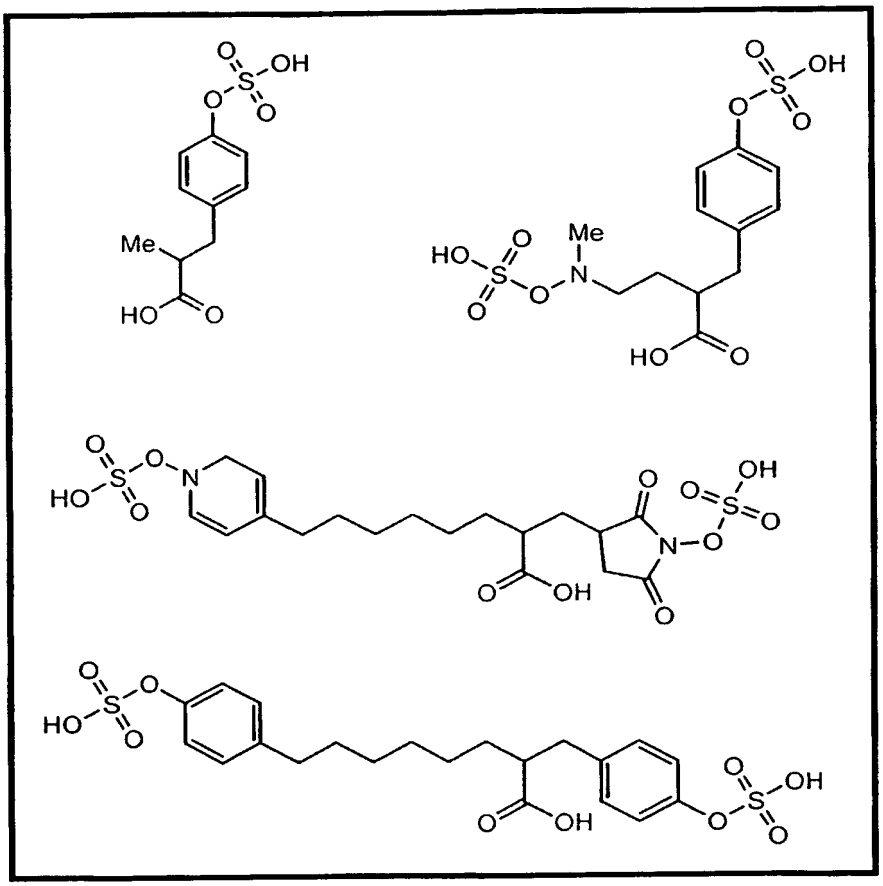


FIGURE 3B

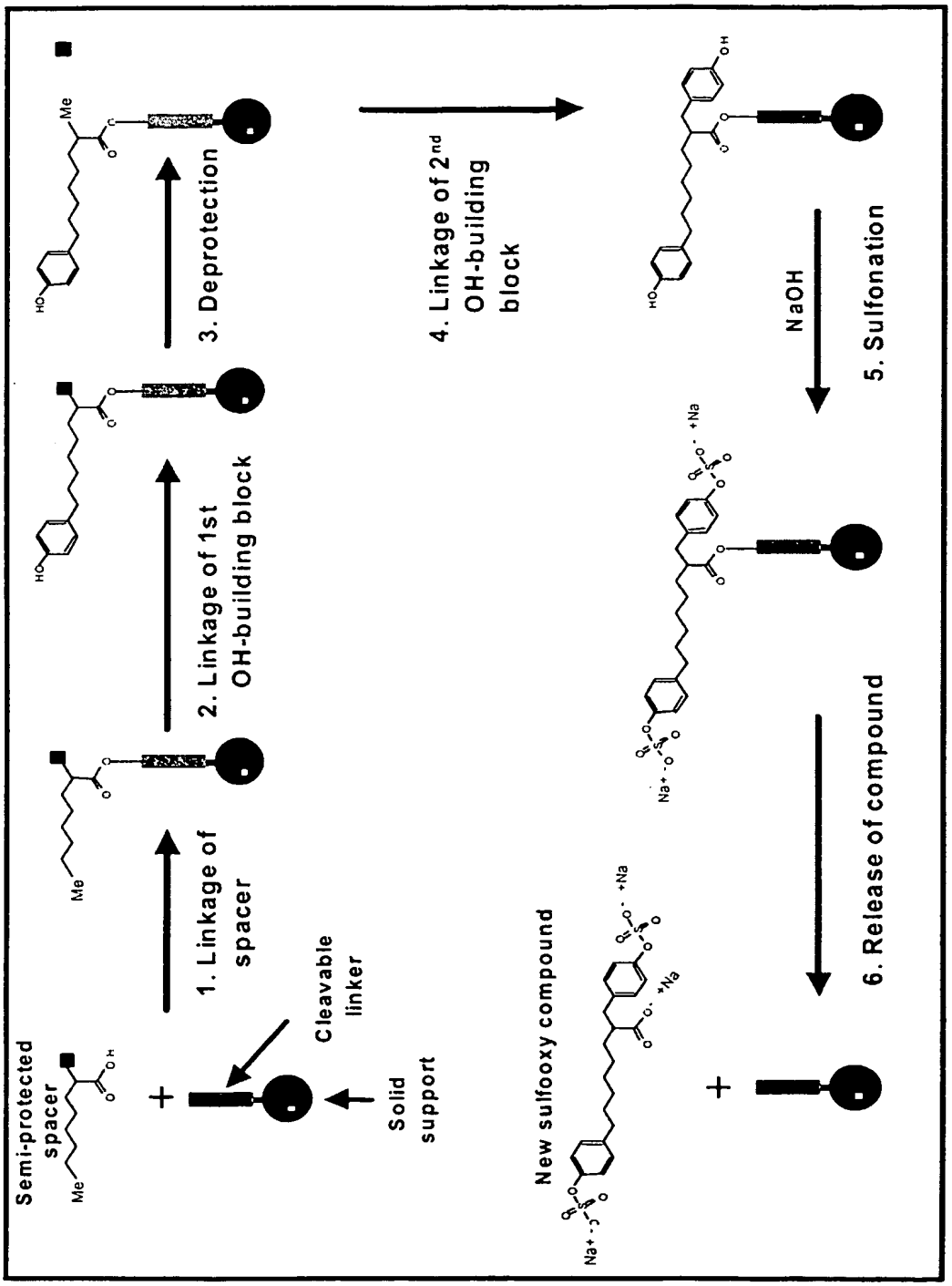
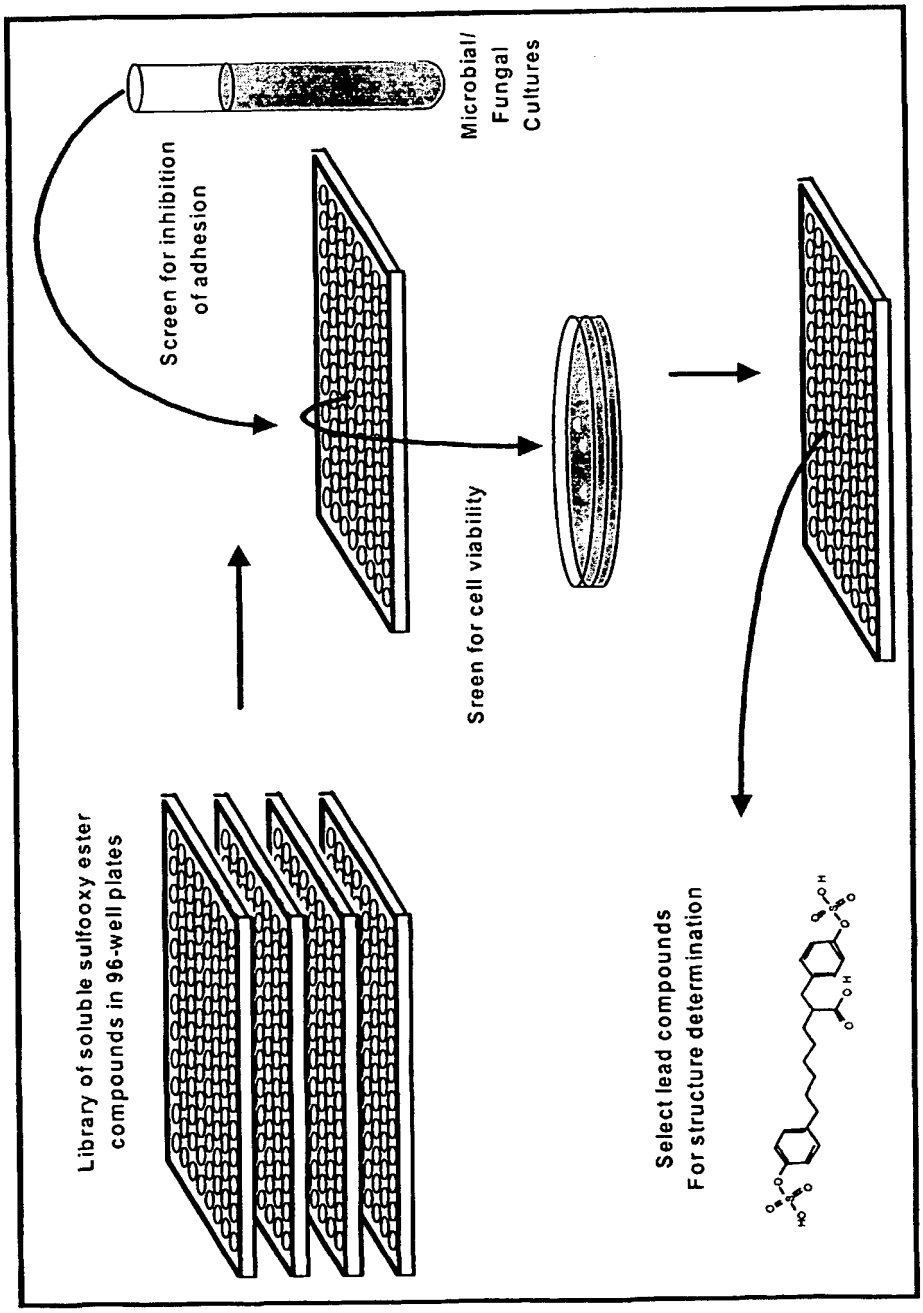


FIGURE 4

FIGURE 5



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(21) International Application Number: PCT/US02/07426

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(71) Applicant *(for all designated States except US)*: **CERNO BIOSCIENCES, LLC.** [US/US]; 87 Dartmouth Street, Boston, MA 02116 (US).

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(74) Agents: **ARNOLD, Beth, E.** et al.; Foley Hoag LLP, 155 Seaport Boulevard, Boston, MA 02210 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
27 November 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/072020 A3

(54) Title: NOVEL ANTI-ADHESIVE COMPOUNDS AND USES THEREOF

(57) Abstract: Compounds which exhibit anti-adhesive properties are described. The compounds may be monomers or polymers. Methods for treating receptor mediated diseases are provided using compounds of the invention. Further methods are provided for crop protection, medical devices and anti-fouling.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/07426

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, STN ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 596 023 B1 (WARNEZ ET AL.) 14 October 1998, pp. 3-4.	1-5
X	EP 0 801 117 A2 (YAMAMORI ET AL.) 15 October 1997, pp. 3-5.	6-10
X	US 5,294,530 A (SETO ET AL.) 15 March 1994, Col. 3, lines 1-68 to col. 4, lines 1-32.	11, 12
X	US 5,208,316 A (YOSHINAGA) 4 May 1993, see Cols. 2 through 20.	11, 12
X	NUZILLARD, J.M. Tetrahedron letters, 1986, Vol. 27, No. 26, pp. 2993-2996.	13
X	US 4,507,235 A (WIINSCH) 26 March 1985, see Cols. 1-6.	15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 NOVEMBER 2002	Date of mailing of the international search report 27 MAY 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ELVIS O. PRICE Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/07426

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3,432,454 A (HIBBARD) 11 March 1969, see Cols. 7-10.	14
X	US 3,331,798 A (HIBBARD) 18 July 1967, see Cols 6-8.	14

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/07426

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

C07C 335/00, 273/00, 275/00, 331/00, 331/00, 303/00, 307/00, 309/00, 311/00, 315/00, 317/00, 305/00, 327/00, 333/00, 329/00; C07D 345/00, 517/00, 205/00, 205/12, 513/00, 205/08, 223/04, 295/00; C08F 2/00, 114/18, 12/20, 14/18, 214/18, 12/30, 126/06, 226/06, 26/06, 132/08, 232/08, 32/08, 124/00, 134/02, 224/00, 234/02, 24/00, 34/02, 138/00, 238/00, 128/02, 228/02, 28/02, 126/02, 226/02, 26/02, 120/54, 120/56, 120/70, 12/28, 126/00, 226/00, 26/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

564/26, 28, 47, 48-52, 79, 80, 82, 83, 84, 86, 88, 89, 90, 91, 92, 95, 96, 97; 568/27, 28, 30-37, 44; 558/20, 24, 25, 26, 29-37, 44, 46-50, 53-58, 230, 232, 234, 241, 242, 248; 540/1, 200, 203, 352, 355-359, 611, 612; 526/72, 242, 248, 258, 259, 260, 266, 285, 286, 287, 288, 301, 302, 303.1, 310, 312

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

564/26, 28, 47, 48-52, 79, 80, 82, 83, 84, 86, 88, 89, 90, 91, 92, 95, 96, 97; 568/27, 28, 30-37, 44; 558/20, 24, 25, 26, 29-37, 44, 46-50, 53-58, 230, 232, 234, 241, 242, 248; 540/1, 200, 203, 352, 355-359, 611, 612; 526/72, 242, 248, 258, 259, 260, 266, 285, 286, 287, 288, 301, 302, 303.1, 310, 312